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AB - The crystal structure of carvedilol (I), prepd. from 4-(2,3-epoxypropoxy)carbazole and 2-MeOC6H4OCH2CH2NH2, was detd. by single-crystal x-ray diffraction. The crystal is composed of a pair of enantiomers, and there are hydrogen bonds O-H-N between the two enantiomers. There are two planes in the mol.

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Synthesis and Crystal Structure of Carvedilol

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ABSTRACT The crystal structure of the title compound carvedilol, $C_{24}H_{25}N_2O_4$ (M_r = 406.47), has determined by single-crystal X-ray diffraction. The crystal is monoclinic with space group $P2_1/c$, a=9.094(1), b=12.754(1), c=18.330(2) Å, β=97.36(1)°, V=2108.5(4) Å^3, Z=4, D_c=1.280 g/cm^3, $F(000)$=864, μ=0.088 mm^{-1} and final R=0.0368, $wR(F^2)$=0.0787 for reflections ($I>2\sigma(I)$). X-ray analysis reveals that the crystal is composed of a pair of enantiomer, and there are hydrogen bonds O(3)—H(30)—N(1) between the two enantimers. There are two planes in the molecule.

Keywords: carvedilol, synthesis, crystal structure

1 INTRODUCTION

Carvedilol, 1-(4-carbazolyloxy)-3-[2-methoxyphenoxy) ethylamino]-2-propanol, is a new β-blocking and vasodilating agent[1]. It had synthesized by F. Wiedemann *et al*[2]. However the report about crystal structure of carvedilol has not been seen. In this paper, we discuss the crystal structure of the carvedilol synthesized[2] by the reaction of 4-(2,3-exoxypropoxy)-carbazole and 2-(2-methoxyphenoxy) ethylamine. Since knowledge of the molecular and crystal structure of carvedilol was considered useful for understanding the mechanism of the action on the receptor, the X-ray crystallographic study was carried out.

2 EXPERIMENTAL

2.1 Synthesis[2] 4-(2,3-Epoxypropoxy)-carbazole (10g, 42mmol) and 2-(2-methoxyphonoxy)-ethylamine (10g, 60 mmol) in 50 ml glycol dimethyl ether were stirred for 25 h at 50 ℃. The reaction mixture was evaporated to dryness in a Rotavapor and the residue was stirred in 115ml toluol, 35 ml cyclohexane and 40 ml ethyl acetate, and recrystallized from ethyl acetate with the use of activecharcoal. 10.4 g(61%) of the title compound were afforded. The single crystals suitable for X-ray analysis were obtained from the mixture solvent of toluol, cyclohexane and

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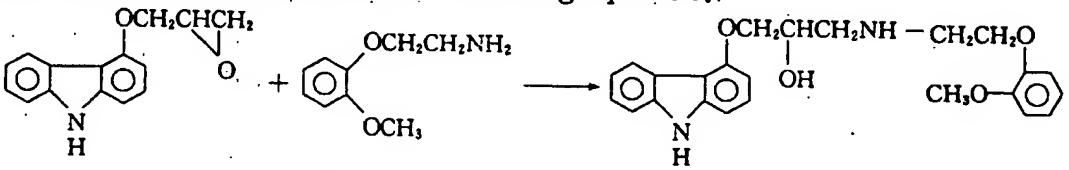
ethyl acetate. mp: 114～115 ℃; Calcd. for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found C, 70.75; H, 6.60; N, 6.72. IR(KBr): ν (N—H, O—H)3346(s), (aryl-H)3087(w), 1609(s), 1588(s), 1503(s), 1447(s) cm^{-1}. NMR: δ_H 1.8 (s, 2H, O—H, $N_{(1)}$—H), 3.1 (m, 4H, $C_{(9)}H_2NC_{(10)}H_2$), 3.8 (s, 3H, OCH_3), 4.2 (m, 5H, $C_{(12)}H_2C_{(11)}H$, $C_{(8)}H_2$), 6.7 (d, 1H, $C_{(15)}H$), 6.9 (s, 4H, $C_{(3-6)}H_4$), 7.1 (d, 1H, $C_{(16)}H$), 7.4～7.2 (m, 4H, $C_{(22-24)}H_3$), 8.20 (d, 1H, $N_{(2)}H$), 8.30(d, 1H, $C_{(14)}H$). MS: m/z 406.2(M^+, 17.7%).

2.2 Structure determination A single crystal with dimensions of 0.66mm × 0.52mm × 0.52mm was selected for X-ray diffraction analysis. All intensity data were collected on a Siemens P_4 diffractometer with graphite monochromated Mo$K\alpha$(λ =0.71073 Å) radiation using ω scan mode. A total of 4081 reflections were collected in the range of $1.95<\theta<24.96°$ at the temperature of 295 K, of which 2096 independent observed reflections with $I>2\sigma(I)$ were used in the structure determination and refinement. The structure was solved by direct methods and succeeding difference Fourier synthesis. A full-matrix least-squares refinement gave final R = 0.0368 and wR=0.0787 with $W=1/[\sigma^2(F_o)^2+(0.0501P)^2]$ and $P=[\max(F_o^2, 0)+2F_o^2]/3$, $(\Delta/\sigma)_{max}$=0.004, S=0.860. The program for structure solution and refinement is SHELXTL 5.03.

3 RESULTS AND DISCUSSION

The title compound was prepared from 4-(2,3-epoxypropoxy)-carbazole and 2-(2-methoxyphonoxy) ethylamine as following equation:



1 2 Carvedilol

The ORTEP plot of the carvedilol with the H atoms is shown in Fig. 1. The unit cell packing of the carvedilol is shown in Fig. 2. Atomic coordinates and thermal parameters are listed in Table 1. The selected bond lengths and angles are given in Table 2 and Table 3, respectively.

Fig. 2 shows that the crystal is composed of a pair of enantiomers, C(11) is a chiral carbon. The angle of O(3)—C(11)—C(10) is 110.5(2)°, that of C(12)—C(11)—C(10) is 110.4(2)°, which are larger than normal 109.5(2)°, the angle of O(3)—C(11)—C(12) is 107.13°, which is slightly less than normal 109.5°. The atoms C(1), O(1), C(2), C(3), C(4), C(5), C(6), C(7) are on one plane, plane equation: $-2.846X+12.021Y-1.391Z+4.9410=0$. While the atoms C(13), C(14), C(15), C(16), C(17), C(18), N(2), C(19), C(20), C(21),

C(22), C(23), C(24) are on the another plane. plane equation $-2.470X+11.564Y-5.228Z+2.1566=0$.

Table 1. Atomic Coordinates and Thermal Parameters(Å²)

Atom	*x*	*y*	*z*	*Ueq*	Atom	*x*	*y*	*z*	*Ueq*
O(1)	0.6502(1)	−0.2750(1)	−0.1120(1)	0.069	C(10)	0.5423(2)	−0.0937(2)	0.1254(1)	0.061
O(2)	0.8405(1)	−0.2127(1)	−0.0057(1)	0.067	C(11)	0.4035(2)	−0.0314(2)	0.0987(1)	0.056
O(3)	0.3346(2)	−0.0714(1)	0.0299(1)	0.075	C(12)	0.2915(2)	−0.0409(2)	0.1528(1)	0.050
O(4)	0.3617(1)	−0.0015(1)	0.2218(1)	0.061	C(13)	0.2817(2)	0.0031(1)	0.2803(1)	0.055
N(1)	0.6482(2)	−0.0943(1)	0.0719(1)	0.058	C(14)	0.1396(2)	−0.0352(2)	0.2810(1)	0.070
N(2)	0.3756(2)	0.1060(1)	0.4609(1)	0.068	C(15)	0.0697(2)	−0.0232(2)	0.3439(1)	0.080
C(1)	0.5335(3)	−0.2973(3)	−0.1699(2)	0.096	C(16)	0.1358(2)	0.0251(2)	0.4059(1)	0.078
C(2)	0.7837(2)	−0.2442(1)	−0.1312(1)	0.054	C(17)	0.2802(2)	0.0608(1)	0.4056(1)	0.058
C(3)	0.8180(3)	−0.2439(2)	−0.2018(1)	0.073	C(18)	0.3543(2)	0.0498(1)	0.3436(1)	0.049
C(4)	0.9535(3)	−0.2108(2)	−0.2156(1)	0.088	C(19)	0.5017(2)	0.0899(1)	0.3632(1)	0.049
C(5)	1.0573(3)	−0.1773(2)	−0.1605(2)	0.084	C(20)	0.5114(2)	0.1234(1)	0.4368(1)	0.056
C(6)	1.0243(2)	−0.1758(2)	−0.0875(1)	0.070	C(21)	0.6419(3)	0.1617(2)	0.4745(1)	0.072
C(7)	0.8873(2)	−0.2091(1)	−0.0737(1)	0.052	C(22)	0.7628(3)	0.1668(2)	0.4378(1)	0.079
C(8)	0.8994(2)	−0.1381(2)	0.0482(1)	0.065	C(23)	0.7563(2)	0.1371(2)	0.3648(1)	0.072
C(9)	0.7931(2)	−0.1338(2)	0.1041(1)	0.064	C(24)	0.6274(2)	0.0986(2)	0.3270(1)	0.059

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Selected Bond Lengths (Å)

Bond	Dist.	Bond	Dist.	Bond	Dist.	Bond	Dist.
O(1)−C(1)	1.429(3)	N(2)−C(17)	1.374(2)	C(8)−C(9)	1.497(3)	C(17)−C(18)	1.400(2)
O(1)−C(2)	1.365(2)	N(2)−C(20)	1.382(2)	C(10)−C(11)	1.518(2)	C(18)−C(19)	1.437(2)
O(2)−C(7)	1.368(2)	C(2)−C(3)	1.370(2)	C(11)−C(12)	1.514(2)	C(19)−C(20)	1.407(2)
O(2)−C(8)	1.424(2)	C(2)−C(7)	1.394(2)	C(13)−C(14)	1.383(2)	C(19)−C(24)	1.398(2)
O(3)−C(11)	1.430(2)	C(3)−C(4)	1.357(3)	C(13)−C(18)	1.394(2)	C(20)−C(21)	1.384(2)
O(4)−C(12)	1.431(2)	C(4)−C(5)	1.360(3)	C(14)−C(15)	1.395(3)	C(21)−C(22)	1.362(3)
O(4)−C(13)	1.372(2)	C(5)−C(6)	1.408(3)	C(15)−C(16)	1.363(3)	C(22)−C(23)	1.385(3)
N(1)−C(9)	1.462(2)	C(6)−C(7)	1.371(2)	C(16)−C(17)	1.391(3)	C(23)−C(24)	1.374(2)
N(1)−C(10)	1.459(2)						

Table 3. Selected Bond Angles (°)

Angle	(°)	Angle	(°)	Angle	(°)
C(1)−O(1)−C(2)	117.9(2)	O(2)−C(8)−C(9)	106.3(2)	C(16)−C(17)−C(18)	121.6(2)
C(7)−O(2)−C(8)	118.40(14)	N(1)−C(9)−C(8)	111.4(2)	C(13)−C(18)−C(17)	119.5(2)
C(12)−O(4)−C(13)	118.95(14)	N(1)−C(10)−C(11)	112.4(2)	C(13)−C(18)−C(19)	133.4(2)
C(9)−N(1)−C(10)	111.74(14)	O(3)−C(11)−C(10)	110.5(2)	C(17)−C(18)−C(19)	107.0(2)
C(17)−N(2)−C(20)	109.7(2)	O(3)−C(11)−C(12)	107.13(14)	C(18)−C(19)−C(20)	106.83(14)
O(1)−C(2)−C(3)	124.1(2)	C(10)−C(11)−C(12)	110.4(2)	C(18)−C(19)−C(24)	134.7(2)
O(1)−C(2)−C(7)	115.83(14)	O(4)−C(12)−C(11)	106.8(2)	C(20)−C(19)−C(24)	118.5(2)
C(3)−C(2)−C(7)	120.0(2)	O(4)−C(13)−C(14)	125.6(2)	N(2)−C(20)−C(19)	108.0(2)
C(2)−C(3)−C(4)	119.9(2)	O(4)−C(13)−C(18)	115.32(14)	N(2)−C(20)−C(21)	129.9(2)
C(3)−C(4)−C(5)	121.3(2)	C(14)−C(13)−C(18)	119.1(2)	C(19)−C(20)−C(21)	122.1(2)
C(4)−C(5)−C(6)	119.9(2)	C(13)−C(14)−C(15)	119.6(2)	C(20)−C(21)−C(22)	117.7(2)
C(5)−C(6)−C(7)	118.7(2)	C(14)−C(15)−C(16)	122.7(2)	C(21)−C(22)−C(23)	121.8(2)
O(2)−C(7)−C(2)	114.8(1)	C(15)−C(16)−C(17)	117.4(2)	C(22)−C(23)−C(24)	120.9(2)
O(2)−C(7)−C(6)	125.1(2)	N(2)−C(17)−C(16)	129.9(2)	C(19)−C(24)−C(23)	119.0(2)
C(2)−C(7)−C(6)	120.1(2)	N(2)−C(17)−C(18)	108.5(2)		

The X-ray crystallographic analysis shows that there is a hydrogen bond O(3)−H(30)−N(1) between the two enantiomers, the distance of O(3)−N(1) is 2.837

Å, and the bond length O(3)—H(3) is 1.139 Å, hydrogen bond length of H(30)—N(1) is 1.730 Å. The angle of O(3)—H(30)—N(1) is 173.1°.

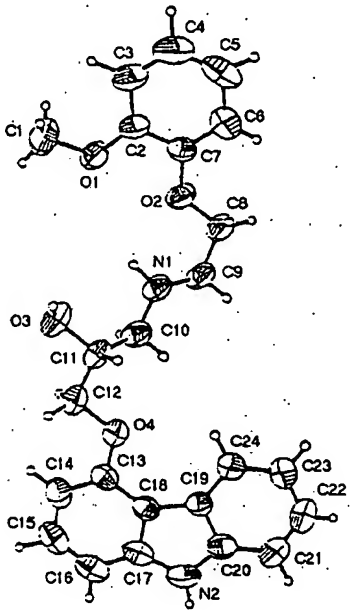


Fig. 1 Structure of carvedilol

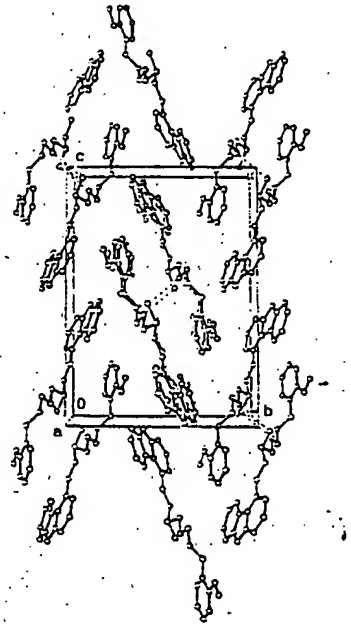


Fig. 2 Packing of the molecules in a unit cell

In vitro in vestigations with the purified stereoisomers of carvedilol show that β_1-adrenoceptor blockade can be attributed primarily to the S(—)-enantiomer. In contrast, both enantiomers exhibit similar α_1-adrenergic blocking activity[3]. Thus, the configuration of chiral carbon C(11) is related to the structure of β_1-adrenoceptor, and not related to the structure of α_1-adrenoceptor. The following illustration was thought[4] as structure-activity relationship of carvedilol. The data of this paper will be useful for understanding the activity center of α_1-adrenoceptor and β_1-adrenoceptor.

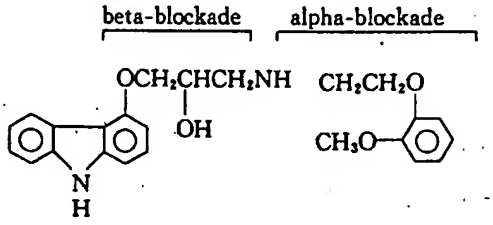


Fig. 3 Structure-activity relationship of carvedilol

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